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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/690,775	08/01/96	FELDMANN	M	KIR92-01A4

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EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 09/01/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 6/10/98

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1,5-10, 13-18, 21-31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1,5-10, 13-18, 21-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 11, 14
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644, Group 1640, Technology Center 1600.

2. Applicant's amendment, filed 6/10/98 (Paper No. 13), is acknowledged.
Claims 2, 3, 11, 12, 19 and 20 have been canceled. Claim 4 has been canceled previously.

Claims 1, 5-10, 13-18, 21-31 are pending.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed ½/98 (Paper No.).
The rejections of record can be found in the previous Office Action (Paper No.).

4. Applicant's arguments, filed 6/10/98 (Paper No. 13), concerning priority of the instant claims back to USSN 07/958,248 have been fully considered but are not found convincing. Applicant has pointed out support for certain limitations of the instant claims to USSN 07/958,248.

However, applicant has not pointed out written support for other limitations of the instant claims.

For example, the instant limitations of "anti-tumor necrosis factor "alpha" antibody; "binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO: 2) of hTNFα"; "competitively inhibits binding of TNFα to monoclonal cA2"; "monoclonal antibody cA2" do not receive priority to USSN 07/958,248 as well as USSN 08/403,785 and PCT/US94/00462. These "limitations" appear to receive priority to USN 08/607,419, filed 2/28/96.

In addition, the instant limitations drawn to modes of administration encompassing "simultaneously", "sequentially" and "multiple doses" do not appear to receive written support or priority to USSN 07/958,248 as well as USSN 08/403,785 and PCT/US94/00462. In addition to written description of these terms per se, it does not appear that these various modes of administration as they encompass the instant combination of anti-TNF antibodies (or TNF antagonists) and methotrexate are supported in USSN 07/958,248 as well as USSN 08/403,785 and PCT/US94/00462. Again, these "limitations" appear to receive priority to USN 08/607,419, filed 2/28/96.

Applicant asserts that the priority of the anti-TNf antibody cA2 are patentable even if the priority date indicated above is correct.

If applicant desires priority prior to 2/28/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

5. Upon review of the instant file, formal drawings, filed 9/98/97 (Paper No. 9) are acceptable.

6. Claims 1, 5-9 and 31 are rejection under 35 U.S.C. § 112, first paragraph, enablement with respect to the breadth of autoimmune or inflammatory diseases targeted with the combination of anti-TNFα antibody and methotrexate essentially for the reasons of record set forth in the previous office Action (Paper No. 10).

Applicant's arguments, filed 6/10/98 (Paper No. 13), have been fully considered but are not found convincing. Applicant's arguments and the examiner's rebuttal are essentially the same as of record concerning the breadth of autoimmune and inflammatory diseases targeted by the claimed methods. In addition, applicant argues that the claimed methods are only drawn to those diseases wherein TNFα plays an important role in the disease. However, as pointed out in the last Office Action; Natanson et al. (Ann Int Med., 1994) teach that anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF could be harmful (see Anticytokine Therapies). Therefore, it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation and distinct differences in diseases which can be targeted by anti-TNFα antibody and methotrexate. Applicant's arguments are not found persuasive.

Applicant is invited to consider providing objective evidence of a representative number of examples of autoimmune or inflammatory diseases wherein the use of anti-TNFα antibody and methotrexate appears to be effective in a predictive manner. However, applicant is reminded that the instant specification discloses that the instant inflammatory diseases encompass autoimmune diseases, viral, bacterial, parasitic infections, malignancies and neurogenerative diseases as useful targets (see page 3, for example).

7. Claims 1, 5-10, 13-18, 21-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Le et al. (U.S. Patent No. 5,656,272) and Aggarwal et al. (U.S. Patent No. 5,672,347) in view of Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989) of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991), Brahn et al. (Arthritis Rheum, 1992); Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3) essentially for the reasons of record set forth in Paper No. 10).

Applicant's arguments, filed 6/10/98 (Paper No. 13),have been fully considered but are not found convincing. Applicant's reliance on asserted unexpected results of the combination of anti-TNFα antibody and methotrexate over each agent alone as disclosed in Examples 1 and 2 of the instant specification is acknowledged. Applicant asserts that the magnitude of these results in the treatment of autoimmune or inflammatory disease could not have reasonably predicted from the cited references, as illustrated in the instant Examples. Applicant argues that there is nothing in the record that the ordinary artisan would reasonably conclude that such a dramatic effect would be expected by combination therapy with methotrexate and anti-TNFα antibody

In contrast to applicant's assertions, consideration of the disclosed results were considered .

Applicant argues that the cited references alone of in combination do not provide an expectation of success or being effective in treating an autoimmune or inflammatory disease in an individual comprising co-administering methotrexate and an anti-TNFα antibody (or TNF anti-TNFα antibody antagonist).

Also, applicant's arguments rely, in large part, to asserted synergistic effects disclosed in the instant examples, however it is noted that such effects were observed with certain patient populations with certain dosing. Such particular patient populations and particular dosing regimens are not claimed. Also, it is noted that such effects observed with certain patient populations with certain dosing regimens does not discount the well known use and expectation of success in combining therapeutic agents to treat diseases.

For example, it is noted that Borigini et al. (Balliere's Clinicla Rheumatology, 1995) (1449) discloses in a review on combination therapy that it was art known that conventional therapies had their limitations, particularly in certain patient populations and that the ordinary artisan was motivated with an expectation of success in combining conventional therapies with agents that inhibit specific events in inflammation (see entire document).

As pointed out previously, the prior art did teach the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that in instances, this combination permits one agent to be used in lesser amounts, thereby counteracting any toxic effects. Also, the prior art did teach efficacy of anti-TNFα antibody in treating patients treated with conventional therapy at the time the invention was made. The prior art also taught the use of anti-TNFα antibody in patients who were resistant to conventional therapy with methotrexate. Therefore it appears that the prior art and the instant Examples rely on showing the efficacy of anti-TNFα in similar patient populations and that treatment with an anti-TNFα antibody such as cA2 in an adjunctive and/or concomitant therapy to conventional therapy was expected to be an important and efficacious therapeutic approach for treating patients. Also in contrast to applicant's assertion, the concomitant use of immunosuppression with antibody therapy was expected to reduce the immunogenicity of therapeutic antibodies and to increase bioavailability of such antibodies at the time the invention was made.

Applicant's arguments concerning the secondary references are acknowledged, however the combination of prior art references do provide the expectation of success in combining methotrexate and an anti-TNFα antibody in treating various inflammatory and autoimmune diseases encompassed by the claimed methods for the reasons of record.

In contrast to applicant's arguments, given the prior art of record, the ordinary artisan would reasonably conclude a therapeutic effect would be expected by combination therapy with methotrexate and anti-TNFα antibody; applicant is invited to consider the combination of references cited in the New Grounds of Rejection below.

Applicant's reliance on certain therapeutic effects with certain dosing does not obviate the motivation and expectation of success in treating autoimmune or inflammatory disease with a highly effective anti-TNFα antibody together with conventional therapies such as methotrexate, as evidenced of record. such as anti-TNF. Again, it is noted that the prior art recognized the same or similar advantages of treating the same or similar patient populations to achieve the same or similar therapeutic effects with the same combination of antiinflammatory agents, encompassed by the claimed methods. That certain patient populations were resistant to conventional therapy does not discount the use of said conventional therapy in

combination with other effective agents to achieve a desired end result. Targeting different elements of an inflammatory response as well as the expectation of success with such combination therapy was known and practiced at the time the invention was made by the ordinary artisan.

Applicant's arguments are not found persuasive.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Patent Examiner
Group 1640
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August 27, 1998

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